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HEMOLYTIC STREPTOCOCCI IN THE FAUCIAL TONSIL AND THEIR SIGNIFICANCE AS SECONDARY INVADERS

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The recognition of hemolytic streptococci in recent measles epidemics as the chief cause of the fatal complications of empyema and bronchopneumonia has led many observers to investigate the frequency and habitat of these organisms both in patients and in healthy individuals. As a result, many data, some of a confusing nature, have been rapidly accumulating. In the winter of 1917 numerous reports on the frequency of the hemolytic streptococcus in the oropharynx were published from the army camps where streptococcal bronchopneumonia and empyema were prevalent. Levy and Alexander[1] found hemolytic streptococci in swabs of the pharynx in 14.8% of 489 new recruits, while in a company of healthy men at camp for six months they were found in 83.2%. Irons and Marine[2] found hemolytic streptococci in the pharynx of 70% of healthy men in the latter part of the epidemics of acute respiratory infections at Camp Custer. Fox and Hamburger[3] reported the same organism in the pharynx of 15% of a group of normal men early in the measles epidemic and six months later in 83% of a similar company. Cole and MacCallum[4] found the streptococci in the pharynx of 21.4% of individuals isolated with suspected tuberculosis. It is evident from these data that it is important to know the incidence and variations of hemolytic streptococci in normal and diseased throats.

The voluminous work prior to 1903 on the frequency of streptococci in the normal mouth is of little value because a satisfactory medium for differentiating the viridans types of streptococci from the hemolytic was not employed until the introduction of the blood-agar plate method.

Received for publication Dec. 31, 1918.

[1] Jour. Am. Med. Assn., 1918, 70, p. 1827.

[2] Ibid., p. 687.

[3] Ibid., p, 1758.

[4] Ibid., p. 1147.

Brailorsky-Lounkevitz,[5] in a study of the flora of the normal mouth, noted the appearance of the Streptococcus pyogenes in one infant within 10 hours after birth and in another within 16 hours. Ruediger[6] found hemolytic streptococci in 59% of 51 normal throats. Smillie[7] described streptococci of the hemolytic type in 50% of 100 normal throats. In a series studied by us to be referred to later, hemolytic streptococci were found in 58% of 24 normal individuals. In all of these studies swab cultures were made from the pharynx or the surface of the tonsils.

Some years ago one of us[8] noted that hemolytic streptococci occurred frequently in pure or predominating numbers in the crypts of 55 of 61 pairs of excised tonsils showing simple hypertrophy, and similarly in 31 of 38 tonsils from cases of arthritis and endocarditis. It was at that time indicated that swab cultures were of limited value in finding hemolytic streptococci. The statement was also made "that hemolytic streptococci may occur in the crypts and on the surface of tonsils not only in ordinary tonsillar infections, but also in normal throats; that these streptococci often cannot be distinguished from the streptococci found in the tonsils of patients suffering from joint troubles."

In a more recent study[9] of streptococci in tonsillar crypts it was noted that hemolytic streptococci were present in predominating numbers in cultures from the epithelial surfaces lining the crypts of excised hypertrophied tonsils, whereas in the actinomyces-like granules often found in the crypts streptococci of the viridans type predominated. Just recently Nichols and Bryan[10] report that they found hemolytic streptococci in the crypts of 75% of 100 pairs of extirpated tonsils, often in pure and predominating numbers, and in 28% of swab cultures of normal throats as compared with 50% of direct crypt cultures.

In the present work a study was made of swab cultures of the pharynx and tonsillar surfaces just before extirpation, and from the crypts of the excised tonsils from the same individuals immediately after extirpation with particular reference to the frequency and predominance of the hemolytic streptococcus. The patients, 100 in all, were chiefly children from 5 to 16 years of age who presented hyperplastic but not markedly diseased tonsils. Examination revealed no evidences of recent acute inflammation, fever or subjective symptoms of sore throat. The tonsils probably represent a closer approach to the normal than any other type of tonsil for which enucleation is indicated. Five adults who gave a history of repeated attacks of sore throat are included in the series. Grossly, the tonsils, when examined after excision, showed little or no change excepting that of hyperplasia. Frequently, firm actinomyces-like granules were found in the crypts. Pus was seldom encountered, but not infrequently the crypts contained a small amount of a thin, slightly turbid exudate. In a few instances soft yellow masses filled a crypt which in smears revealed amorphous material, often cholesterin crystals, and few or no bacteria.

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[5] Ann. de l'Instit. Pasteur, 1915, 29, p. 379.

[6] Jour. Infect. Dis., 1906, 3, p. 755.

[7] Ibid., 1917, 20, p. 45.

[8] Davis, D. J.: Jour. Infect. Dis., 1912, 10, p. 148.

[9] Pilot, I., and Davis, D. J.: Jour. Infect. Dis., 1918, 23, p. 562.

[10] Jour. Am. Med. Assn., 1918, 71, p. 1812.

Three separate swabs were applied, one to the pharynx, and one over each tonsillar surface, immediately before administration of the anesthetic. Cultures were made from these swabs within 1-4 hours. The tonsils, each wrapped separately in sterile gauze, were obtained immediately after extirpation. Macerated tonsils were discarded because of the impossibility of obtaining uncontaminated cultures of the crypts. Plain extract agar with a reaction of 0.3 was melted and defibrinated human blood added in proportion of 1 of the latter to 10 of the former. The melted blood agar tubes were inoculated directly with the swabs and poured into petri dishes. Each tonsil was incised cleanly with a sterile knife and the bottom of the crypts exposed. Material was collected from 3 or 4 crypts on a platinum loop and introduced directly into the melted blood-agar tubes which were poured into plates. Usually a dilution was made of the cultures both from the swabs and the tonsils. The plates were incubated aerobically at 37.5 C., and were observed at the end of 24 and 48 hours. Readings were made from the first plate in most instances. The dilutions were reserved for the isolation of pure cultures. In the study of the plates particular attention was given to the hemolytic colonies characteristic of streptococci as differentiated from the nonhemolytic streptococci which grew as small grayish-white colonies surrounded by a green or grayish-green zone. Staphylococci, diphtheroids and other organisms which occasionally cause hemolysis were eliminated by direct smear and study of subcultures.

The hemolytic streptococci grew as small round, discrete, grayish-white colonies surrounded by a clearly defined zone of hemolysis 2 to 4 mm. wide, which microscopically showed no red blood corpuscles. The colonies correspond to the Beta type of Smith and Brown.[11] From one patient similar colonies with clearly defined zones of hemolysis only 1-1.5 mm. wide were encountered. Occasionally colonies appeared in 24 hours with a green zone, and in 48 hours formed an indistinct narrow zone of hemolysis outside of the green zone. These colonies were classified under the nonhemolytic streptococci. Subcultures of the hemolytic streptococci were made on blood-agar slants. Small, discrete, biconvex, glistening colonies developed causing a distinct wide zone of hemolysis along the streak of inoculation.

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[11] Jour. Med. Research, 1914, 31, p. 455.

The results of the cultures of the swabs and the crypts of the tonsils in 20 cases are indicated for comparison in detail in Table 1. These 20 are fairly representative of the entire group, and a glance at the table will indicate the great predominance of the hemolytic streptococci in the crypts.

TABLE 1

STREPTOCOCCI IN TONSILS

No.	Age	Sex	Pharynx		Right Tonsil Surface		Left Tonsil Surface		Right Tonsil Crypts		Left Tonsil Crypts	
			Hemolytic Streptococci	Non-hemolytic Streptococci	Hemolytic Streptococci	Non-hemolytic Streptococci	Hemolytic Streptococci	Non-hemolytic Streptococci	Hemolytic Streptococci	Non-hemolytic Streptococci	Hem. olytic Streptococci	Non-hemolytic Streptococci
2	12	F	+	++	+	++	+	++	++++	+	++++	+
3	13	F	+	++++	+	++++	+	++++	++	++	+	++++
4	15	F	+	++	+	++	+	++	+	++	+	++
5	14	F	+	++	+	++	+	++	++++	0	++++	0
6	6	F	0	++++	+	++	0	++++	++++	0	++++	0
7	7	F	+	++	+	++	+	++	+++	0	+++	0
8	13	M	0	+++	0	++++	0	++++	+++	0	++++	+
9Y	14	M	+	++++	+	++++	+	++++	++++	0	++++	0
10	7	F	+	++++	0	++++	+	++++	++	0	++	0
11	7	F	+	++++	+	++++	+	++++	++++	+	++++	0
12	6	F	+	++	+	++	+	++	++	+	++	+
13	10	M	+	++++	+	+++	+	+++	+++	+	++	++
14	13	M	+	++	+	++	+	++	++++	+	++++	+
15	12	F	+	++++	+	++++	+	++++	++	++	++	++
16	7	F	+	++++	+	++++	+	++++	++++	+	++++	0
17	16	M	0	++++	+	++++	0	++++	++	0	++	++
19	12	F	0	++++	+	++++	+	++++	++	+	++	+
20	12	M	+	++++	++	++	+	++++	++++	+	++	++
21	13	F	0	++++	0	++++	0	++++	++++	++++	++	++
22	12	M	+	++++	0	++++	0	++++	+	++++	++	++

TABLE 2

PERCENTAGE OF HEMOLYTIC STREPTOCOCCI IN SWABS AND CRYPT CULTURES OF 100 TONSILS

	Per Cent.
Swab cultures—	
Pharynx	43
Left tonsillar surface	49
Right tonsillar surface	59
One or both tonsillar surfaces	61
Cultures from crypts of excised tonsils—	
Right tonsil	92
Left tonsil	92
One or both tonsils	97

In Table 2 the frequency of hemolytic streptococci from the different sources is summarized. In cultures of the pharynx the colonies were few in number, constituting from 1-10% of the total. In no instance were they predominant. Similarly, in cultures from the tonsillar surfaces hemolytic streptococci were slightly more numerous, but still relatively few in number except in one instance where they were predominent. It is worthy of note that hemolytic streptococci were found on tonsillar surfaces in a decidedly higher percentage

(61%) than in the pharynx (43%). Of interest, too, is the occurrence of hemolytic streptococci in the crypts in 97% as compared with 61% on the tonsillar surfaces leaving 36 instances in which the streptococci were found in direct cultures of the crypts of excised tonsils from which surface swab cultures were negative. In all cases of positive swab cultures of the pharynx and tonsils, hemolytic streptococci were invariably found in larger numbers in the crypts. Another striking feature is the frequent predominance of hemolytic streptococci over all other micro-organisms in the crypts as indicated in Table 3.

TABLE 3

HEMOLYTIC STREPTOCOCCI IN THE CRYPTS OF EXCISED TONSILS

	Per Cent.
In Pure Culture—	
In both tonsils	11
In right or left	16
Predominating—	
In both tonsils	30
In right or left	17
In moderate number in both or in one tonsil	13
Few in both tonsils	10
None in both	3
None in one tonsil (present in the other)	6

TABLE 4

ORGANISMS OTHER THAN STREPTOCOCCI FOUND IN AEROBIC CULTURES OF THROAT AND TONSILLAR CRYPTS

	Pharynx and Surface of Tonsil, %	Crypts of Excised Tonsils, %
Staphylococcus	40	30
Micrococcus catarrhalis	11	3
Pneumococcus	20	5
Diphtheroids	6	4
B. diphtheriae	1	0
Micrococcus tetragenus	1	0
B. mucosis	2	3

In Table 4 are listed the organisms encountered in the aerobic cultures. Pneumococci were differentiated from nonhemolytic streptococci by the appearance of typical colonies and by direct smear. No attempt was made at further differentiation by cultural and serologic studies since this would constitute a problem in itself. Nonhemolytic streptococci were found constantly as the predominating organism in 98% of pharyngeal cultures, and in 97% of swab cultures of tonsillar surfaces. In the crypts they were found in 73%, and here they were less numerous than in the surface cultures as is shown in Table 1. It is probable that the nonhemolytic streptococci would be more common and numerous in the crypts if anaerobic cultures were also made, for we have demonstrated strongly anaerobic green-producing streptococci in connection with the actinomyces-like granules of the tonsils.[9]

In ascites-carbohydrate broth the hemolytic streptococci produce a flaky sediment with the small flocculi settling on the sides of the tube while the supernatant fluid with few exceptions remains clear. Rarely a slight turbidity is produced. Smears reveal gram-positive cocci usually in long chains. In most instances the cocci are spherical and only a few display a tendency to flattening of the opposing surfaces. Ninety strains were inoculated into the 4 differential sugar mediums—lactose, salicin, mannite and inulin. The medium was enriched with ascites fluid 1 part to 4 parts of 1% carbohydrate broth to which litmus solution was added as indicator. Readings were made at the end of 4 and 10 days. All strains fermented lactose, all but 5 fermented salicin, only 2 fermented mannite, and none inulin. According to Holman's[12] classification, they would fall chiefly in the Streptococcus pyogenes group; 1 strain would be classed as the Streptococcus infrequens, another as the Streptococcus hemolyticus.

TABLE 5

HYDROGEN-ION DETERMINATIONS IN BROTH CULTURES OF HEMOLYTIC STREPTOCOCCI*

Strains No.	P_H+ Electrometric	P_H+ Colorometric
77	5.3	5.3
19	5.4	5.4
68	5.2	5.2
B	5.3	5.2
9Y	5.3	5.2
116	5.3	5.2
129	5.2	5.2
127	5.2	5.2
51	5.3	5.2
16I	5.3	5.2
97	5.3	5.2
66	5.2	5.2
3	5.2	5.2
101	5.3	5.2
98	5.2	5.2

* We are indebted to Dr. Horry Jones for these determinations.

In litmus milk all strains produced acid. The clot formed spontaneously in five instances. Of the remainder, clotting was induced by gently heating to the boiling point for 1-5 minutes in all but 10 strains. This reaction in litmus milk is an important aid in differentiating the human strains from the far less pathogenic hemolytic streptococci of the lacticus group commonly found in raw milk. The milk streptococci, as shown by one of us,[13] turns litmus tube rapidly white, coagulating the milk and forming a firm clot spontaneously. The strains from the tonsils correspond to the human type of hemolytic streptococci.

Further confirmation is furnished by the determination of the limiting hydrogen-ion concentration of the tonsil strains in carbohydrate broth cultures (1% lactose or dextrose ascitic broth cultures incubated 96 hours). The results are given in Table 5. The P_H values correspond to those of Ayres, Johnson and Davis[14] who, employing dextrose yeast peptone medium, found a P_H value of 5.4 to 6.0 for pathogenic streptococci as compared with value of 4.6 to 4.7

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[12] Jour. Med. Research, 1916, 34, p. 377.

[13] Davis, D. J.: Jour. Infect. Dis., 1916, 19, p. 236.

[14] Jour. Infect. Dis., 1918, 23, p. 290.

for the nonpathogenic streptococci. Smillie,[7] using dextrose infusion broth, found a limiting hydrogen-ion concentration of 5.5 for 4 strains of hemolytic streptococci.

TABLE 6

STREPTOCOCCI IN NORMAL THROATS

Source	Number of Cases	Hemolytic Streptococci		Nonhemolytic Streptococci, Percentage Positive
		Number Positive	Percentage Positive	
Normal Throats:				
Pharynx	24	6	25	100
Surface of tonsils	24	14	58	100
Gums	24	0	0	100
Nose	24	0	0	16
Streptococci in Throats of Individuals without Tonsils:				
Pharynx	19	3	15.8	100
Surface of tonsils	19	3	15.8	100
Gums	19	0	0	100
Nose	3	0	0	0

Twenty-two strains of hemolytic streptococci were selected at random and one blood-agar slant (incubated 48 hours) culture suspended in physiologic salt solution was injected intravenously in young rabbits. One animal died within 4 days, and four others within the 4th to the 10th day. The remaining 7 rabbits all had lesions and were killed on the 10th day. The rabbits lost from 10-130 gm. in weight rapidly. Within 48 hours several joints became enlarged. The lesions were chiefly a seropurulent or markedly purulent polyarthritis of the wrists, phalangeal joints, knees, ankles, occasionally the hip and shoulder joints. In one instance the right sternoclavicular joint was involved. Subpericardial, subpleural and subperitoneal hemorrhages occurred frequently. Verrucose endocarditis of the mitral valves was noted in three instances, of the tricuspid once, serofibrinous pericarditis and peritonitis once each. Tenosynovitis and hemorrhages into the skeletal muscles were occasionally encountered. In two instances (9 and 16) there appeared unilateral purulent iritis and iridocyclitis with pus in the anterior chamber from which hemolytic streptococci were recovered. The lesions correspond closely to those produced by streptococi isolated from the tear sac and tonsils by others.[15, 16] In three animals three-fourths and one-half of one blood-agar slant were fatal. In another, one-fourth tube produced a slight joint lesion. In the fatal cases hemolytic streptococci identical with those injected were almost uniformly recovered from the joints and the heart blood. In rabbits surviving for 10 days the affected joints were usually sterile and the heart blood gave no growth.

The morphological and cultural characteristics of these hemolytic streptococci are identical with those of the hemolytic streptococci isolated from empyema, bronchopneumonia, and other fatal streptococcus infections.[10] The uniformity of the strains in these respects together with their uniform virulence for rabbits points strongly to

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[15] Rosenow: Jour. Infect. Dis., 1915, 17, p. 402.

[16] Irons, Brown and Nadler: Ibid., 1916, 18, p. 315.

the homogeneity of the human streptococcus hemolyticus group as recently determined by Kinsella and Smith[17] by means of complement fixation tests.

Hemolytic streptococci, being found as we have shown in swab cultures in 61% and in the crypts of 97% of excised tonsils showing chiefly hyperplasia, the question arises as to the frequency of the same organisms in the crypts of the normal tonsil. It has been stated that in swab cultures of normal tonsils Ruediger[6] found hemolytic streptococci in 59% and Smillie[7] in 50%; and in cultures direct from crypts Nichols and Bryan[10] found them in 50%. These figures are strikingly similar, and vary only 2-11% from the percentages with which hemolytic streptococci were isolated from the surface of hyperplastic tonsils. It is difficult to make cultures direct from the crypts with the tonsil in situ because of the almost unavoidable contamination with bacteria from the tonsillar surface and about the outlet of the crypt. This method therefore tends to increase the number of green-producing streptococci and other bacteria in the cultures and is not reliable.

In order to obtain further evidence whether the tonsils are a source of hemolytic streptococci normally, especially the crypts, a comparative study was made of the pharynx and tonsils of healthy individuals as compared with the throat of normal persons whose tonsils had been totally or partially removed some time previously. This comparison was made with a view to determine the possible influence of such removal on the occurrence of hemolytic streptococci in the throat.

Swab cultures were first made from the pharynx and the surface of each tonsil, from the gum margin and the nose, of 24 healthy persons who gave no history of recent sore throat and whose tonsils showed no gross evidence of acute or chronic inflammation. This group was composed of medical students, a few hospital interns, and several patients recently admitted to the surgical ward following trauma. They ranged in age from 20-30 years. Cultures were made in 10% blood agar by the poured plate method and the plates incubated at 37.5 C. for 48 hours. Readings were made at the end of 24 and 48 hours.

In cultures of the pharynx from this group hemolytic streptococci were found in 25%; in cultures of the surface of the tonsils in 58%. In all instances the number of colonies of hemolytic streptococci was less than 10% of the total colonies on the plate. In no instance were they found on the gum margin or in the nose. Nonhemolytic streptococci were noted in all the cultures from the pharynx and tonsils and were particularly numerous from the gums (Table 6).

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[17] Jour. Exper. Med., 1918, 28, p. 169.

In a second series similar cultures were made from 24 individuals of the same age (20-30) whose tonsils had been removed. In all but two the date of excision was from 6 months to 8 years previously; in two instances the tonsils had been removed 2 and 3 weeks previously, and the surfaces appeared congested and edematous. In 3 other persons remnants of tonsillar tissue appeared on either one or both sides. There are therefore nineteen instances in which no visible remnants of tonsils and no evidence of inflammation appeared. Cultures from these nineteen revealed hemolytic streptococci in scant numbers in three (15.8%) while nonhemolytic streptococci were present approximately in the same numbers as in the first series. In the two recently operated throats hemolytic streptococci were found in both. Two of the three individuals having remnants of tonsils gave hemolytic streptococci.

TABLE 7

Incidence of Hemolytic Streptococci in the Throat and Sputum in Various Infectious Diseases

Disease	Investigators	Number of Cases	Percentage Giving Hemolytic Streptococci
Scarlet fever	Anthony	29	76
Scarlet fever	Ruediger	75	96
Scarlet fever	Wohl and Detweiler	27	100
Measles	Anthony	24	83.3
Measles	Ruediger	9	55.5
Measles	Cole and MacCallum	69	56.5
Measles	Simonin	45	60
Measles	Davis	23	100
Measles	Levy and Alexander	388	77.1
Influenza	Mathers	61	75.4
Influenza	Wohl and Detweiler	31	100
Influenza	Moody and Capps	30	100
Influenza	Nuzum, Pilot and others	100	37
Influenza	Hastings and Niles	39	28.6
Lobar pneumonia	Cole and MacCallum	26	57.7
Lobar pneumonia	Stone and others	59	50
Lobar pneumonia	Hastings and Niles	66	25.5

Comparing the two series it is seen that hemolytic streptococci were present in 15.8% of the throats of individuals without tonsils as compared with 58% of throats with normal tonsils. Excision of the tonsils therefore seems to reduce the frequency of hemolytic streptococci without any effect on the nonhemolytic; the results further indicate that the tonsils are the chief foci harboring hemolytic streptococci. Nichols and Bryan report the disappearance of hemolytic streptococci from the throat in 27 of 31 patients 11 days after extirpation of the diseased tonsils. Since remnants of tonsillar tissue may harbor hemolytic streptococci it is possible in the three instances showing these organisms in the second series that the foci may have been in tonsil remnants not readily visible.

The high frequency of hemolytic streptococci in the human throat may explain the important rôle these organisms play as secondary invaders in a multitude of diseases. As is well known in acute infectious diseases like scarlet fever, measles, small-pox, etc., in most instances death is not due to the primary etiologic factor, but to secondary infections, especially the streptococcus. It is significant that in various acute infections characterized by an acute inflammation of the nasopharyngeal passages and by angina, the hemolytic streptococcus can be demonstrated in large numbers in cultures from the throat, and that the same organism is more often found in the fatal complicating lesions than any other organism. In table 7 are given the results of different investigators in which streptococci definitely of the hemolytic type were demonstrated in throats or sputum in various diseases.

Hektoen[18] found long chain streptococci in the blood of 12 of 100 cases before death in mild as well as in severe cases. Dick and Henry[19] isolated hemolytic streptococci from the blood, lymph glands, spleen and urine of fatal cases. Pearce[20] frequently recovered streptococci which could not be differentiated from ordinary Streptococcus pyogenes, and regarded these as the most common cause of the complications of bronchopneumonia, otitis media, and other general infections. Councilman[21] and others noted numerous masses of streptococci on the surface and in the substance of the necrotic lesions of the mouth. Streptococcus was the most common organisms in the lungs, heart and other organs of fatal cases. Perkins and Pay[22] likewise found the Streptococcus pyogenes in 95% of the fatal cases, and recovered the same organism from the blood in 1-4 days before death in 8 of 13 cases. The latter investigators showed further that there was a diminution of complement by demonstrating a decreased bacteriolytic action on B. coli and B. typhosus of the serum of affected patient. Thompson by the same method found a loss of complement especially in cases where streptococci were later isolated from fatal lesions. He believed that the specific contagion of variola caused a diminution of complement which predisposed to secondary local and general infections.

The Streptococcus pyogenes is commonly associated with the diphtheria bacillus in the lesions of diphtheria. Hilbert[23] believed that a symbiotic relationship existed in cultures inoculated with both organisms. Councilman, Mallory and Pearce,[24] in their extensive studies in diphtheria, found the

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[18] Jour. Am. Med. Assn., 1903, 40, p. 685.

[19] Jour. Infect. Dis., 1914, 15, p. 85.

[20] Med. and Surg. Reports of Boston City Hosp., 1899, p. 39.

[21] Studies on the Path. and Etiol. of Variola and Vaccinia, Boston, p. 67.

[22] Jour. Med. Research, 1903, 10, p. 163.

[23] Quoted from Hiss and Zinsser, A Textbook of Bacteriology, 1918, p. 31.

[24] Jour. Boston Soc. Med. Sc., 1900, 5, p. 139.

Streptococcus pyogenes to be the most frequent organism associated with the diphtheria bacillus in the complicating lesions of the lung, middle ears, the accessory sinuses and the serous cavities, and found streptococci even more frequently than the diphtheria bacillus in the heart blood, liver, spleen and kidneys.

In measles (Table 7) hemolytic streptococci have been found with great frequency in the swab cultures of the pharynx and tonsils both in past and recent epidemics. The percentage varies from 55-100%, and the organisms are stated to occur often in predominating numbers. The complications of empyema and bronchopneumonia were apparently caused by the same organism as reported by Levy and Alexander,[1] Fox and Hamburger,[3] Stone,[25] Clendening,[26] Beals and others,[27] Lorey,[28] Craig,[29] Cole and MacCallum.[4] The general opinion of most of these observers is that the Streptococcus hemolyticus is carried by droplet infection from a carrier to susceptible measles patients. These organisms according to present bacteriologic methods are similar in cultural characteristics and biologic reactions to the streptococci isolated from normal and diseased tonsils. Two possibilities present themselves to explain the epidemic form of the streptococcus complications. Either the measles virus had attained unusual virulence, rendering the patient highly susceptible to the hemolytic streptococci already present in the crypts of the tonsil, or that a strain of hemolytic streptococcus may have been greatly enhanced in its invasive properties by passage through several hosts until new susceptible individuals succumb to streptococcus empyema and bronchopneumonia without a primary measles infection.[26] Tunnicliff[30] has shown that there is a diminution in the phagocytic activity of the leukocytes during the early stages of measles when a leukopenia exists. Hektoen[31] states that "the frequency of streptococcus infection in this disease depends in some degree on the reduction in the powers to react against streptococci."

Acute respiratory infections with influenza-like symptoms have been reported in which hemolytic streptococci were found constantly in the throat and sputum often in predominating numbers (Table 8). Mathers,[32] Wohl and Detweiler, Moody and Capps,[33] Müller and Seligmann[34] were inclined to believe that these epidemics were due primarily to the Streptococcus hemolyticus. In the pandemic of 1889-90 the micro-organisms most constantly found were the streptococcus and the pneumococcus. In 1911, Hastings and Niles[35] reported 39 cases, hemolytic streptococci predominating in the sputum of 11. In the present pandemic (1918) the streptococcus is no doubt playing an important rôle in causing complications. Nuzum and Pilot[36] isolated hemolytic streptococci from the lungs in 43%, and occasionally from the heart blood (8 of 36 necropsies) and the pleural fluid. It was obtained in pure culture in 3 of 15 positive cultures from puncture of the lungs during life. Friedlander and others[37] noted it in the lungs in 46.7%, while Synnott and Clark[38] found it commonly in the sputum and in the lungs. From personal observations we have been surprised by the small number of hemolytic streptococci and certain other organisms of the throat in the very early stages of the disease. Indeed, hemolytic streptococci were found less often than in the normal throat (31%). In the later stages, however, the organism appeared more frequently and in larger numbers until in individuals with complications of pneumonia they were often found to be predominant in the throat and, less frequently, in the sputum. In the lungs they were usually associated with the pneumococcus or the influenza bacillus, but often appeared in pure culture in the heart blood and serous cavities suggesting a terminal streptococcus invasion of the blood stream.

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[25] Arch. Int. Med., 1918, 22, p. 409.
[26] Am. Jour. Med. Sc., 1918, 156, p. 575.
[27] Jour. Infect. Dis., 1918, 23, p. 475.
[28] Ztschr. f. Hyg. u. Infektionskr., 1909, 63, p. 135.
[29] Jour. Am. Med. Assn., 1905, 44, p. 1187.
[30] Jour. Infect. Dis., 1918, 22, p. 462.
[31] Jour. Am. Med. Assn., 1918, 71, p. 1201.
[32] Jour. Infect. Dis., 1917, 21, p. 1.
[33] Jour. Am. Med. Assn., 1916, 66, p. 1696.
[34] Berl. klin. Wchnschr., 1911, 42, p. 1636.
[35] Jour. Am. Med. Assn., 1918, 71, p. 1562.
[36] Jour. Am. Med. Assn., 1918, 71, p. 1562.

In pneumonia of the lobar type hemolytic streptococci are commonly encountered in the throat and sputum in addition to the pneumococcus (Table 7). Clendening reports lobar pneumonia to be complicated by hemolytic streptococcus infection in 14% of 319 cases. In blood cultures immediately after death in lobar pneumonia streptococci have been occasionally demonstrated. (Richey and Goehring.[39]) In lobar pneumonia as in measles the question has arisen in connection with the epidemic form of streptococcus infections whether the complications are due most often to the streptococci already present in the tonsils of the patient; or, when epidemics are prevalent, to streptococci of enhanced virulence transmitted from patient to patient.

In other infectious diseases hemolytic streptococci have been frequently found. They were noted by Davis[40] in the throat of 57 of 61 cases of whooping cough, and in 8 of 11 cases of varicella.

In long standing diseases in which the state of resistance becomes progressively lowered the Streptococcus pyogenes is the most frequent cause of terminal infection. It is common to find at necropsy terminal infection with no distinct focal lesions. In his study on terminal infections, Flexner[41] commonly encountered streptococci and mentions the tonsil as the possible atrium of infection in some cases. Gwyn and Harris[42] recognized the streptococcus pyogenes in antemortem blood cultures as agonal invaders in cases of chronic parenchymatous nephritis, cirrhosis of the liver, leukemia, endocarditis and pneumonia. In cultures postmortem these organisms were isolated in the corresponding cases, and also in two cases of typhoid fever and in a case of ulceration of the larynx and esophagus which had given negative cultures antemortem. Strauch,[43] in 2,000 blood cultures postmortem, found the Streptococcus pyogenes altogether in 548; in 460 of this number it occurred alone. His series included cases of the acute exanthemata, chronic wasting diseases, and various forms of acute and chronic tuberculosis. In cultures taken immediately after death Fredette[44] encountered the same organism in 42 of 119 individuals with such diseases as leukemia, chronic endocarditis, pneumonia, appendicitis and others. Richey and Goehring[39] in a similar study recovered the organism in 14 of 19 positive cultures from 55 cases of chronic wasting diseases. Flexner showed that the bactericidal effect of serum from patients affected with chronic renal or cardiorenal diseases was less against Staphylococcus aureus than that or normal serum. Later Longcope[45] examined the serum of 17 similar patients and observed a reduced bactericidal action on B. coli and B. typhosus, especially in those who subsequently succumbed to terminal infections. It would seem that the diminution of protective substances in the blood is to a large extent the underlying basis for the occurrence of terminal infections.

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[37] Jour. Am. Med. Assn., 1918, 71, p. 1652.

[38] Ibid., 1918, 71, p. 1816.

[39] Jour. Med. Research, 1918, 38, p. 420.

[40] Jour. Infect. Dis., 1906, 3, p. 1.

[41] Jour. Exper. Med., 1896, 1, p. 558.

[42] Jour. Infect. Dis., 1902, 2, p. 514.

[43] Ztschr. f. Hyg. u. Infektionskr., 1910, 65, p. 183.

[44] Jour. Lab. and Clin. Med., 1916, 2, p. 180.

The regularity with which hemolytic streptococci can be demonstrated in the throats of patients affected with acute exanthemata, acute respiratory infections, diphtheria, pneumonia, etc., suggests that the common source of these organisms is from some preexisting focus which harbors these bacteria. It seems unlikely that the same organism could be so regularly introduced from without in such a variety of primary diseases. Streptococci of enhanced virulence may occasionally be transmitted in epidemic form by direct or indirect contact, by droplet infection and by milk, as in septic sort throat; but these routes are probably relatively unusual, although at times no doubt they exist and may prove most serious.

Three possible factors may be concerned in the production of secondary streptococcus infections. (1) The existing dormant organisms in the tonsil or throat may become enhanced in their virulence through symbiosis or in some unknown way by the primary virus (measles, scarlet fever, smallpox), or by the bacteria such as B. diphtheriae, pneumococcus or influenza bacillus. (2) They may become active through the diminution of the resistance of the local tissues of the respiratory passages. (3) They may attain increased invasive powers through the lowering of the general resistance of the host overwhelmed by an acute or chronic toxemia. Probably all three factors are combined in certain diseases, though one factor often appears to be more important than the others. Thus, in acute respiratory and throat infections, streptococci seem to spread from the tonsillar crypts to the adjacent mucous surfaces, descend into the bronchi and lungs, and enter the blood stream from these tissues. In chronic diseases, on the other hand, the diminution of the resisting power of the blood may admit the streptococci directly into the circulating blood stream without any marked local changes in the throat.

CONCLUSIONS

Hemolytic streptococci are common in the normal and diseased throat. The chief foci of these organisms are the crypts of the tonsils.

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[45] Univ. of Penn. Med. Bull., 1902, 15, p. 331.

Hemolytic streptococci were recovered by swab cultures in sparse numbers from the pharynx and tonsillar surfaces in 61% of throats, chiefly children with hyperplastic tonsils; and from the crypts of the excised tonsils of the same individuals in 97%, usually in predominating numbers. Swab cultures are therefore unreliable in determining the incidence of this organism in the respiratory tract.

The frequency of hemolytic streptococci is decidedly less in the throats of persons whose tonsils have been extirpated than in the throats of persons with normal tonsils.

These streptococci agree in the main in their morphology, cultural characteristics, fermentation reactions and pathogenicity for rabbits, and are practically identical with hemolytic streptococci isolated from various human pathologic sources.

Hemolytic streptococci from the crypts of the tonsils are probably the most important source of the streptococcus complications of the various acute infectious diseases, and of the terminal infections.